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Publication Title:

CALCIUM PHOSPHATE/SULPHATE-BASED BONE IMPLANT COMPOSITION

Abstract:

Abstract of WO02087649

A bone implant composition, the composition comprising calcium sulphate and slowly soluble sources of calcium, orthophosphate and hydroxyl ions. The composition may be provided in powder or granulated form. Data supplied from the esp@cenet database - Worldwide

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Published:
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WO 02/087649 A1

(54) Title: CALCIUM PHOSPHATE/SULPHATE-BASED BONE IMPLANT COMPOSITION

(57) Abstract: A bone implant composition, the composition comprising calcium sulphate and slowly soluble sources of calcium, orthophosphate and hydroxyl ions. The composition may be provided in powder or granulated form.

CALCIUM PHOSPHATE / SULPHATE-BASED BONE IMPLANT COMPOSITION

This invention concerns a bone implant composition, and a method of forming a bone graft.

In orthopaedic and dental surgical applications there is a great need for biocompatible and bioresorbable implant material which can be conveniently and effectively used as a bone substitute. This includes bone lost due to periodontal disease, ridge augmentation, sinus elevation, bone defects or cavities due to trauma, disease or surgery and spinal fusions. Following implantation the bone substitute is ideally resorbed in a time frame which is consistent with its replacement by new vital bone.

The bone graft material of preferred choice is autograft, i.e. the patients own bone, since this is totally biocompatible, is not subject to an immune response or disease transmission and has good osteogenic capacity. However, its source is limited, it requires a second surgical procedure for harvest and there are often donor site morbidity problems.

Allograft bone is usually considered an acceptable alternative since it is more readily available and has a reasonable level of efficacy. However, it has the potential for disease transmission and since it is 'foreign' tissue there is the potential for immunological reactions. In addition, it is a material variable in its properties, due to donor source (often elderly people with osteoporotic bones) and processing variability. This makes prediction of clinical outcome difficult when allograft is used. Delayed healing is a frequent complication.

According to the present invention there is provided a bone implant composition, the composition comprising calcium sulphate and slowly soluble sources of calcium, orthophosphate and hydroxyl ions.

The source of the ions is preferably provided by compounds which are slowly soluble in water, and preferably compounds where the water solubility at

room temperature is less than 5g per litre, desirably less than 1g per litre, and more desirably less than 0.1g per litre.

The source of the calcium ions may be the calcium sulphate alone, or may be provided by one or more of: calcium carbonate, calcium phosphate, calcium oxide, calcium fluoride, calcium citrate, calcium stearate, or dolomite.

The calcium sulphate may be in the form of dihydrate, hemi-hydrate, soluble anhydrite or insoluble anhydrite. The ratio of calcium sulphate to all other compounds in the composition is preferably between 0.2 and 2 parts by weight.

The composition may also comprise a medicament, and desirably in an effective therapeutic amount. The medicament may comprise any of: an antibiotic, an anti-cancer agent, or bone morphogenic protein.

The source of orthophosphate ions may be one or more of: hydroxyapatite, alpha tricalcium phosphate, beta tricalcium phosphate, dicalcium phosphate, tetracalcium phosphate or magnesium orthophosphate. The source of orthophosphate ions may be in the form of a micro-porous granular solid. The granules may have a particle size in the range 0.2 - 5.00mm. The source of orthophosphate may be in the form of a micro-porous granular solid component.

The source of the hydroxyl ions may be one or more of: calcium oxide, insoluble anhydrite, calcium hydroxide, magnesium oxide, magnesium hydroxide, zinc oxide, zinc hydroxide, or basic magnesium carbonate.

In the composition the ratio of basicity to orthophosphate is preferably between 0.0 and 1.0 molar.

The composition may be in the form of a powder which can be mixed with water or an aqueous solution to form a usable paste.

Alternatively, the composition may be in the form of granules or pellets. The composition may be formed into pellets using a tablet press.

The invention also provides a method of forming a bone graft, the method comprising using a bone implant composition according to any of the preceding ten paragraphs.

When in powder form the composition may be mixed with water or an aqueous solution to form a putty or paste prior to application. The putty or paste may be applied to a surgical site by a suitable applicator such as a syringe. Alternatively the putty or paste may be applied to a mould and allowed to set prior to presentation to the surgical site.

Where the composition is in the form of granules or pellets, the granules or pellets can be packed into a bone cavity.

Embodiments of the present invention will now be described by way of example only.

Example 1

A powdered mixture was prepared according to the following composition:-

1.25g beta tricalcium phosphate
0.63g calcium sulphate alpha hemihydrate
0.05g magnesium oxide

The beta tricalcium phosphate particles have a size of 250 - 500 microns.

The mixture was blended with 0.85ml of a 1% potassium sulphate solution to give a paste which was used to fill a periodontal pocket.

Example 2

A powdered mixture was prepared according to the following composition:-

35.0g beta tricalcium phosphate granules with a particle size of 1 - 2mm diameter.

17.5g calcium sulphate dihydrate
2.2g magnesium oxide
0.80g calcium stearate

The mixture was pressed into pellets 3mm diameter by 2.5mm deep using a tablet press. The pellets were used to fill a bone cavity.

Example 3

A powdered mixture was prepared according to the following composition:-

35.0g alpha tricalcium phosphate
14.0g anhydrous calcium sulphate - insoluble form
10.0g basic magnesium carbonate
0.1g zinc oxide

The mixture was pressed into pellets using a tablet press.

Example 4

A powdered mixture was prepared according to the following composition:-

10.0g beta tricalcium phosphate particles
5.0g calcium sulphate alpha hemihydrate powder
0.5g magnesium oxide

The beta tricalcium phosphate particles have a size range of 1 - 2mm.

The mixture was blended with 9.5ml of water and compacted into 6mm diameter cylindrical moulds where it was allowed to set. The set pellets were removed from the moulds and allowed to dry. These were used to fill a bone cavity.

Example 5

A powdered mixture was prepared according to the previous example (Example 4), but including 5% by weight of the antibiotic gentamycin which was added to the powdered mix prior to moulding.

There is thus described a bone implant composition and a method of using same which provides for considerable advantages. The composition is based upon the following chemical equation:-

$$10Ca^{2+} + 6PO_4^{3-} + 2OH^- = Ca_{10}(PO_4)_6(OH)_2$$

The composition provides a source of ions which precipitate in vivo to provide a poorly crystalline, substituted apatite which closely mimics the natural mineral phase of bone, in contrast to other presently available synthetic bone graft substitutes. Also, the reaction occurs over a time frame commensurate with the body's ability to regenerate new healthy bone. This precipitated hydroxyapatite is amenable to osteoclastic resorption. The calcium sulphate phase initially present resorbs by a simple dissolution mechanism over a period of a few weeks to provide a macroporous structure amenable to vascularisation and invasion by new bony tissue. The calcium sulphate forms a micro-porous barrier which prevents intrusion of unwanted soft tissue (cells) in the immediate post implantation period.

The source of ortho phosphate is preferably a micro-porous granular solid, with a particle size of 0.2 - 5mm. This size range provides for an

intergranule pore size of 100 - 200 microns which is necessary for cell infiltration and vascularization to stimulate new bone in-growth.

Various modifications may be made without departing from the scope of the invention. The calcium ions may be obtained from the calcium sulphate alone, or may also be obtained from calcium stearate as in Example 2, or other calcium compounds such as calcium carbonate, calcium phosphate, calcium oxide, calcium fluoride, calcium citrate or dolomite. In addition or as an alternative to the orthophosphate ions being provided by beta tricalcium phosphate, these ions may be provided by hydroxyapatite, alpha tricalcium phosphate, dicalcium phosphate, tetracalcium phosphate or magnesium orthophosphate.

In the examples the source of hydroxyl ions is magnesium oxide, and also zinc oxide in Example 3. These ions may though additionally or as an alternative be obtained from calcium oxide, insoluble anhydrite, calcium hydroxide, magnesium hydroxide, zinc hydroxide or basic magnesium carbonate. As illustrated in the Examples, the calcium sulphate may be in one or more of the following forms:- alpha hemihydrate, beta hemihydrate, soluble anhydrite, insoluble anhydrite or dihydrate.

The composition may comprise a medicament in an effective therapeutic amount, which medicament may comprise an antibiotic, an anti-cancer agent, or bone morphogenic protein.

Whilst endeavouring in the foregoing specification to draw attention to those features of the invention believed to be of particular importance it should be understood that the Applicant claims protection in respect of any patentable feature or combination of features hereinbefore referred to and/or shown in the drawings whether or not particular emphasis has been placed thereon.

CLAIMS

1. A bone implant composition characterised in that the composition comprises calcium sulphate and slowly soluble sources of calcium, orthophosphate and hydroxyl ions.

2. A composition according to claim 1, characterised in that the source of the ions is provided by compounds which are slowly soluble in water.

3. A composition according to claim 2, characterised in that water solubility of the compounds at room temperature is less than 5g per litre.

4. A composition according to claim 3, characterised in that water solubility of the compounds at room temperature is less than 1g per litre.

5. A composition according to claim 4, characterised in that water solubility of the compounds at room temperature is less than 0.1g per litre.

6. A composition according to any of the preceding claims, characterised in that the source of the calcium ions is the calcium sulphate alone.

7. A composition according to any of claims 1 to 5, characterised in that the source of the calcium ions is provided by one or more of: calcium carbonate, calcium phosphate, calcium oxide, calcium fluoride, calcium citrate, calcium stearate, or dolomite.

8. A composition according to any of the preceding claims, characterised in that the calcium sulphate is in the form of dihydrate, hemi-hydrate, soluble anhydrite or insoluble anhydrite.

9. A composition according to any of the preceding claims, characterised in that the ratio of calcium sulphate to all other compounds in the composition is between 0.2 and 2 parts by weight.

10. A composition according to any of the preceding claims, characterised in that the composition comprises a medicament.

11. A composition according to claim 10, characterised in that the medicament is in an effective therapeutic amount.

12. A composition according to claim 10 or claim 11, characterised in that the medicament comprises any of: an antibiotic, an anti-cancer agent, or bone morphogenic protein.

13. A composition according to any of the preceding claims, characterised in that the source of orthophosphate ions is one or more of: hydroxyapatite, alpha tricalcium phosphate, beta tricalcium phosphate, dicalcium phosphate, tetracalcium phosphate or magnesium orthophosphate.

14. A composition according to any of the preceding claims, characterised in that the source of orthophosphate ions is in the form of a micro-porous granular solid.

15. A composition according to claim 14, characterised in that the granules have a particle size in the range 0.2 - 5.00mm.

16. A composition according to any of the preceding claims, characterised in that the source of the hydroxyl ions may be one or more of: calcium oxide, insoluble anhydrite, calcium hydroxide, magnesium oxide, magnesium hydroxide, zinc oxide, zinc hydroxide, or basic magnesium carbonate.

17. A composition according to any of the preceding claims, characterised in that in the composition the ratio of basicity to orthophosphate is between 0.0 and 1.0 molar.

18. A composition according to any of the preceding claims, characterised in that the composition is in the form of a powder which can be mixed with water or an aqueous solution to form a usable paste.

19. A composition according to any of claims 1 to 17, characterised in that the composition is in the form of granules or pellets.

20. A composition according to claim 19, characterised in that the composition is formed into pellets using a tablet press.

21. A method of forming a bone graft, characterised in that the method comprises using a bone implant composition according to any of the preceding claims.

22. A method according to claim 21 when dependent on claim 18, characterised in that when in powder form the composition is mixed with water or an aqueous solution to form a putty or paste prior to application.

23. A method according to claim 22, characterised in that the putty or paste is applied to a surgical site by a suitable applicator such as a syringe.

24. A method according to claim 22, characterised in that the putty or paste is applied to a mould and allowed to set prior to presentation to the surgical site.

25. A method according to claim 21 when dependent on claim 19 or claim 20, characterised in that when the composition is in the form of granules or pellets, the granules or pellets can be packed into a bone cavity.

26. Any novel subject matter or combination including novel subject matter disclosed herein, whether or not within the scope of or relating to the same invention as any of the preceding claims.

INTERNATIONAL SEARCH REPORT

PCT/GB 02/01986

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L27/42 A61C8/00 A61F2/28 A61F2/46 A61L24/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61C A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 824 087 A (ASPDEN RICHARD MALCOM ET AL) 20 October 1998 (1998-10-20)	1-5, 7-15, 17-25
A	column 1, line 19 - line 52 column 2, line 26 - line 31 column 3, line 15 - line 31 column 6, line 27 - line 33 column 7, line 3 - line 21 column 7, line 52 - line 57 column 8, line 22 - line 25 claims 5-8	16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2002	15/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hars, J

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OHURA K ET AL: "Resorption of, and bone formation from, new beta-tricalcium phosphate-monocalcium phosphate cements: an in vivo study." JOURNAL OF BIOMEDICAL MATERIALS RESEARCH. UNITED STATES FEB 1996, vol. 30, no. 2, February 1996 (1996-02), pages 193-200, XP001095806 ISSN: 0021-9304 abstract page 193 page 196, right-hand column, paragraph 4 page 197, right-hand column, paragraph 4 table I ---	1-5,7-25
A	PEPELASSI E M ET AL: "Doxycycline-tricalcium phosphate composite graft facilitates osseous healing in advanced periodontal furcation defects." JOURNAL OF PERIODONTOLOGY. UNITED STATES FEB 1991, vol. 62, no. 2, February 1991 (1991-02), pages 106-115, XP001095805 ISSN: 0022-3492 abstract page 107, right-hand column, paragraph 4 - paragraph 5 page 111, right-hand column, paragraph 3 page 113, left-hand column, last line -right-hand column, line 3 ---	1-5,7-25
A	IKENAGA M ET AL: "Biomechanical characterization of a biodegradable calcium phosphate hydraulic cement: a comparison with porous biphasic calcium phosphate ceramics." JOURNAL OF BIOMEDICAL MATERIALS RESEARCH. UNITED STATES APR 1998, vol. 40, no. 1, April 1998 (1998-04), pages 139-144, XP001105176 ISSN: 0021-9304 abstract page 140 page 141, right column, section 'Microscopic results' tables I,II --- -/--	1-5,7-25

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OHURA K ET AL: "Healing of segmental bone defects in rats induced by a beta-TCP-MCPM cement combined with rhBMP-2." JOURNAL OF BIOMEDICAL MATERIALS RESEARCH. UNITED STATES FEB 1999, vol. 44, no. 2, February 1999 (1999-02), pages 168-175, XP001105179 ISSN: 0021-9304 abstract page 168, right-hand column, paragraph 2 -page 169, left-hand column, paragraph 2 page 169, right-hand column, paragraph 3 -page 170, left-hand column, paragraph 1	1-5,7-25

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 02 01986

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 21-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

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Continuation of Box I.2

Claims Nos.: 6,26

Present claim 6 relates to a bone implant composition characterised in that the source of the calcium ions is calcium sulphate alone.
The application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT only for bone implant compositions characterised in that a slowly soluble calcium orthophosphate (beta- or alpha-tricalcium phosphate) in a granular form is included, as the resulting porous intergranular space is necessary for cell infiltration (page 5, last two lines - page 6, line 2). In particular, all examples 1-5 employ calcium orthophosphate.
A bone implant composition characterised in that the source of the calcium ions is calcium sulphate alone according to claim 6 lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claim 6 also lacks clarity (Article 6 PCT).

Present independent claim 26 lacks any characterising feature and solely defines the protected subject matter with vague terms such as 'any novel subject matter' or 'the scope of or relating to the same invention'. A lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of claim 26 impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

PCT/GB 02/01986

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 6,26
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/GB 02/01986

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5824087 A	20-10-1998	AU 2218395 A	30-10-1995
		DE 19581923 T0	12-02-1998
		WO 9527518 A1	19-10-1995
		GB 2301531 A ,B	11-12-1996
		ZA 9502880 A	21-12-1995